

REMARKS

Claims 1, 4, 7, 8, 10-13, and 15-19 are pending.

Applicants thank the Examiner for indicating that claims 7, 8, and 10-12 are allowed.

Claims 1, 4, 13, and 15-19 remain rejected.

Applicants acknowledge the Examiner's rejection of claims 1 and 4 under 35 U.S.C. § 112 ¶1, based on alleged new matter. Applicants respectfully traverse this rejection and have provided specification support for the alleged new matter.

Applicants acknowledge the Examiner's rejection of claims 1 and 4 under 35 U.S.C. § 112 ¶1, based on alleged lack of written description. Applicants respectfully traverse this rejection based on the specification support for the written description.

Applicants acknowledge the Examiner's maintained rejection of claims 1, 4, 13, and 15-19 under 35 U.S.C. § 112 ¶1, based on alleged lack of *enablement*. Applicants have amended claims 1, 2, 13, and 15-19 to recite "diagnostic assay" and have deleted the recitation of "prognostic," and have additionally provided appropriate rebuttal arguments.

No new matter has been added.

Rejections under 35 U.S.C. § 112, ¶1

Alleged new matter:

The Examiner has rejected of claims 1 and 4 under 35 U.S.C. § 112 ¶1, based on alleged new matter in view of recitation of "one or more coordinately methylated CpG dinucleotide sequences within SEQ ID NO:36." Applicants respectfully traverse this rejection.

The specification at page 8, lines 14-22, along with Table II (showing that SEQ ID NO:36 is a CpG island sequence), provides support for coordinately methylated CpG dinucleotide sequences within SEQ ID NO:36. Specifically, the specification recites:

"Additionally, at least 55 of these 103 sequences correspond to CpG islands (based on GC Content and O/E ration); namely [SEQ ID NOS:2, 4, 6, 7, 9-16, 19, 20, 22-33, 35-43, 48, 51-55,

59, 60, 64, 71, 76, 78-81, 84 and 87-90]. Thus, **based on the fact that the methylation state of a portion of a given CpG island is generally representative of the island as a whole**, the present invention further encompassed the novel use of the 55 CpG islands associated with [SEQ ID NOS:2, 4, 6, 7, 9-16, 19, 20, 22-33, 35-43, 48, 51-55, 59, 60, 64, 71, 76, 78-81, 84 and 87-90] in cancer prognostic, diagnostic and therapeutic applications, where a CpG island sequence associated with the sequence of a particular SEQ ID NO is that contiguous sequence of genomic DNA that encompasses at least one nucleotide of the particular SEQ ID NO sequence, and satisfies the criteria of having both a frequency of CpG dinucleotides corresponding to an Observed/Expected Ratio >0.6, and a GC Content >0.5” (emphasis added).

Applicants respectfully contend that the phrase “based on the fact that the methylation state of a portion of a given CpG island is generally representative of the island as a whole” would be understood by one of ordinary skill in the relevant art as coordinate methylation in the context of Applicant’s specification. Moreover, as shown in column 1 of Table II, methylation of the CpG island SEQ ID NO:36 is characterized as hypermethylation. Furthermore, the specification (at page 5, lines 8-11) teaches that “‘Hypermethylation’ refers to the methylation state corresponding to an *increased* presence of 5-mCyt at **one or a plurality** of CpG dinucleotides within a DNA sequence of a test DNA sample, relative to the amount of 5-mCyt found at corresponding CpG dinucleotides within a normal control DNA sample” (emphasis added).

Applicants contend, therefore, that there is adequate written descriptive support for “one or more coordinately methylated CpG dinucleotide sequences within SEQ ID NO:36” as presently recited.

Applicants, therefore, respectfully request that the Examiner’s new matter rejection be withdrawn with respect to claims 1 and 4 as presented herein.

Rejections under 35 U.S.C. § 112, ¶1

Alleged lack of sufficient written description:

The Examiner has rejected of claims 1 and 4 under 35 U.S.C. § 112 ¶1, based on alleged lack of written description in view of “one or more coordinately methylated CpG dinucleotide sequences within SEQ ID NO:36.” Applicants respectfully traverse this rejection.

Applicants point out, in relation to the Examiner’s citing of *University of California v. Eli Lilly*, that Applicants have indeed disclosed a representative genus of coordinately methylated CpG sequences.

The specification at page 8, lines 14-22, along with Table II (showing that SEQ ID NO:36 is a CpG island sequence), provides support for coordinately methylated CpG dinucleotide sequences within SEQ ID NO:36. Specifically, the specification recites:

“Additionally, at least 55 of these 103 sequences correspond to CpG islands (based on GC Content and O/E ration); namely [SEQ ID NOS:2, 4, 6, 7, 9-16, 19, 20, 22-33, 35-43, 48, 51-55, 59, 60, 64, 71, 76, 78-81, 84 and 87-90]. Thus, **based on the fact that the methylation state of a portion of a given CpG island is generally representative of the island as a whole**, the present invention further encompassed the novel use of the 55 CpG islands associated with [SEQ ID NOS:2, 4, 6, 7, 9-16, 19, 20, 22-33, 35-43, 48, 51-55, 59, 60, 64, 71, 76, 78-81, 84 and 87-90] in cancer prognostic, diagnostic and therapeutic applications, where a CpG island sequence associated with the sequence of a particular SEQ ID NO is that contiguous sequence of genomic DNA that encompasses at least one nucleotide of the particular SEQ ID NO sequence, and satisfies the criteria of having both a frequency of CpG dinucleotides corresponding to an Observed/Expected Ratio >0.6, and a GC Content >0.5” (emphasis added).

As discussed above, Applicants contend that the phrase “based on the fact that the methylation state of a portion of a given CpG island is generally representative of the island as a whole” would be understood by one of ordinary skill in the relevant art as “coordinate

methylation” in the context of Applicants’ specification. Moreover, as shown in column 1 of Table II, methylation of the CpG island SEQ ID NO:36 is characterized as hypermethylation. Furthermore, the specification (at page 5, lines 8-11) teaches that “ ‘Hypermethylation’ refers to the methylation state corresponding to an *increased* presence of 5-mCyt at one or a plurality of CpG dinucleotides within a DNA sequence of a test DNA sample, relative to the amount of 5-mCyt found at corresponding CpG dinucleotides within a normal control DNA sample” (emphasis added).

Because SEQ ID NO:36 is a CpG island, and because its sequence is provided (and hence the sequence of every CpG species within SEQ ID NO:36), Applicants respectfully contend that there is adequate written description for recitation of “one or more coordinately methylated CpG dinucleotide sequences within SEQ ID NO:36.”

Applicants, therefore, respectfully request withdrawal of this *written description* rejection.

Rejections under 35 U.S.C. § 112, ¶1

Enablement:

The Examiner has maintained rejections of claims 1, 4, 13, and 15-19 under 35 U.S.C. § 112 ¶1, based on alleged lack of enablement in view of recitation of “a CpG dinucleotide.”

Applicants’ maintained traversal:

Applicants respectfully traverse the Examiner’s rejection. The proper inquiry with respect to scope of enablement under 35 U.S.C. §112, first paragraph, is whether it would require *undue* experimentation to make and use the subject matter as claimed, and, as discussed below in detail, such is not the case.

Relevant Law:

Applicants maintain that to satisfy the enablement requirement of 35 U.S.C. §112, first paragraph, the specification must teach one of skill in the art to make and use the invention without *undue* experimentation. Atlas Powder Co. v. E.I. DuPont de Nemours, 750 F.2d 1569, 224 USPQ 409 (Fed. Cir., 1984). This requirement can be satisfied by providing sufficient disclosure, either through illustrative examples or terminology, to teach one of skill in the art how to make and how to use the claimed subject matter without undue experimentation. This clause does not require “a specific example of everything within the scope of a broad claim.” In re Anderson, 471 F.2d 1237, 176 USPQ 331, at 333 (CCPA 1973), emphasis in original. A patentee is not only entitled to narrow claims particularly directed to the preferred embodiment, but also to broad claims which define the invention without a reference to specific instrumentalities. In re Anderson, at 1241 (citing Smith v. Snow, 294 U.S. 1, 11, 24 USPQ 26, 30 (1935)). Further, because “it is manifestly impracticable for an applicant who discloses a generic invention to give an example of every species falling within it, or even to name every such species, it is sufficient if the disclosure teaches those skilled in the art what the invention is and how to practice it.” In re Grimme, Keil and Schmitz, 124 USPQ 449, 502 (CCPA 1960). There is, therefore, no requirement for disclosure of every species within a genus. Applicants are entitled to claims that are commensurate in scope not only with what Applicants have specifically exemplified, but commensurate in scope with that which one of skill in the art could obtain by virtue of that which the Applicants have disclosed.

Applicants respectfully submit that the Examiner has not established a *prima facie* case of lack of enablement, as the proper inquiry with respect to scope of enablement under 35 U.S.C. §112, first paragraph, is whether it would require *undue* experimentation to make and use the subject matter as claimed. A considerable amount of experimentation is permissible, particularly

if it is **routine experimentation**. As appreciated by the Examiner, the amount of experimentation that is permissible depends upon a number of factors, which include: the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability of the art, and the breadth of the claims. Ex parte Forman, 230 USPQ 546 (Bd. Pat. App. & Int’f 1986); see also In re Wands, 8 USPQ2d 1400 (Fed. Cir. 1988).

Analysis:

Citing *Wands*, the Examiner states that the invention is in a class of inventions characterized as “the unpredictable arts” by the CAFC.

As an initial matter, while Applicants appreciate that chemistry and biology are generally regarded as relatively unpredictable arts, the Examiner acknowledges that the art clearly teaches that certain genes are hypermethylated and this is indicative of certain cancers (citing U.S. Patents 5,552,227, 5,846,712, and 5,856,094). Moreover, the Examiner’s own cited literature articles of record in this case (and as discussed herein below) prove that it was known in the art that CpGs within a CpG island can be coordinately methylated, although, as appreciated by the Examiner, not All CpGs within a CpG island are necessarily coordinately methylated, and coordinately methylated CpGs don’t necessarily need to be adjacent CpG dinucleotide sequences within the CpG island.

Toyota:

We are in agreement with the Examiner that Toyota teaches “examples where CpG islands act independently.” However, independently acting of islands is not the relevant question here. Applicants reassert, reaffirm, and further clarify Applicants’ arguments of record with respect to Toyota. The relevant question is whether particular CpG dinucleotide sequences within a given CpG island behave coordinately, and not necessarily whether ALL, or only adjacent CpG

dinucleotide sequences behave coordinately. Here, the teachings of Toyota are more than in agreement with the Applicants' currently recited claims.

Specifically, Toyota initially describes/defines a large 4Kb region, based on a definition of having a GC content of 0.67; CpG/GpC ratio of 0.78; and a total of 305 CpG sites in a 4-kb region (Toyota at page 4536, column 2, middle of first full paragraph), and divides this 4kb region into 8 subregions. However, Toyota notes that this region is considerably larger than typical CpG islands (Toyota at page 4537, column 2, first full paragraph), and he explicitly concludes that "with regards to hypermethylation in cancer, the CpG-rich region upstream of CACNA1G appears to be composed of two CpG islands that behave independently" (MINT31 regions 1 and 2 corresponding to the upstream CpG island 1; the 5' regions 5-7 of CACNA1G in the downstream CpG island 2; and regions 3, 4 and 5 between CpG island 1 and 2, behaving differently). Toyota concludes (page 4540, at end of the carryover paragraph) that "methylation of MINT 31 appears to be independent of methylation of CACNA1G, suggesting that they are two distinct CpG island regulated by different mechanisms." Significantly, therefore, Toyota teaches that while different CpG islands within a gene area can behave differently or independently, the subregions within a given CpG island, for example regions 1 and 2 of island 1 and regions 5-7 of island 2, behave coordinately and define the behavior of the CpG island which comprises the subregions.

Therefore, Toyota like the vast bulk of art in this area, is fully consistent with the teachings of the present invention which teach that the CpG dinucleotides within a given contiguous CpG island are often coordinately methylated.

The Examiner, at page 7 of the Office Action, states that Toyota, however, "does teach different subregions within a given CpG island, such as regions 5-7 of island 2," that "Toyota teaches that regions 5, 6 7 behaved differently than did regions 1-3," and that methylation within some subregions was "less frequent" or sometimes showed "no detectable methylation." The

Examiner states that different nucleotides within at least one DNA sequence of an island do not necessarily share coordination in their methylation.

Applicants respectfully point out, however, that contrary to the Examiner's position, coordinate hypermethylation within a CpG island requires neither that ALL CpGs within the island are hypermethylated, nor that the coordinately hypermethylated CpGs are adjacent to each other within the CpG island, nor that the CpG island is devoid of "subregions" that might be methylated or coordinately methylated to a lesser extent. Coordinate methylation in the instant sense rather requires CpGs within the CpG island that are differentially coordinately methylated. Applicants, therefore, respectfully contend that the Examiner's comments are not misleading, irrelevant, and inappropriate to the present issue of enablement.

Pao:

Likewise, with respect to the Examiner's comments relating to Pao. The teachings of Pao, that not all CpGs in a CpG island were hypermethylated even when adjacent to CpGs that were hypermethylated (*e.g.*, that some adjacent CpGs were resistant or protected from hypermethylation), does not run counter to Applicants' recitation of coordinately methylated CpGs, because Applicants' recitation does not require that *all* CpGs within a CpG island are coordinately methylated, but rather only that the methylation change (*e.g.*, hypermethylation) of the those CpGs that are differentially methylated between normal and cancer, is a methylation change that is coordinate, so that coordinately differentially methylated CpGs are either up-methylated (hypermethylated to some extent), or down-methylation (hypomethylated to some extent). Applicants' claims reflect the fact that within a particular CpG island, there are CpGs that do undergo a methylation change between cancer and normal that is coordinate (*e.g.*, coordinately hypermethylated). Again, it is irrelevant that some CpGs are protected from, or resist, hypermethylation, for example. The claims are drawn to coordinately methylated CpGs with the

CpG island, and **do not necessarily require that all CpGs, or only adjacent CpGs, are coordinately differentially methylated between normal and cancer**. In fact, the CpGs of Pao follow this pattern in that while not all CpGs participate in differential methylation between normal and abnormal tissue, those that do participate, do so in a generally coordinate way, although the extent of hypermethylation is not identical between differentially methylated CpGs there is nonetheless coordinate methylation in Pao, and therefore Pao, like Toyota, actually teaches coordinate methylation.

Cameron:

Applicants respectfully reassert Applicants' contention that the Examiner's position (i.e., that Cameron allegedly teaches that the p15 CpG island methylation is heterogeneous, and thus does not support that a single dinucleotide may be representative of an entire CpG island) is unsupportable, because the methylation heterogeneity characterized in Cameron relates to heterogeneity in the specific CpGs sites hypermethylated between alleles. That is, like Pao, not all CpGs on both alleles undergo hypermethylation. However, those CpGs that do show hypermethylation are coordinately hypermethylated.

With respect to Cameron et al., the Examiner states that Cameron teaches there was heterogeneity of CpG methylation in the p15 CpG island and that Cameron does not support the argument that a single dinucleotide may be representative of the entire CpG island. Applicants respectfully point out that Applicants' claimed invention is not premised on there being a single dinucleotide that is necessarily representative of ALL the CpGs of an entire CpG island, but rather that CpG island sequences, including those presently claimed, typically comprise coordinately methylated CpG dinucleotide sequences.

Therefore, Applicants respectfully contend that the Examiner's position is not supportable in view of Toyota, Pao, and Cameron, and that these references in fact actually support

Applicants' position of coordinate hypermethylation within a CpG island.

Moreover, given the instant teachings and the state of the art, and fully consistent with Toyota, Pao, and Cameron cited by the Examiner, Applicants contend that it would not entail *undue* experimentation to determine whether any particular CpG dinucleotide of the contiguous CpG island sequence of SEQ ID NO:36 or 37 is coordinately methylated with a CpG of SEQ ID NO:36 or 37. This is precisely what would be expected as described above, and in view of Toyota, Pao, and Cameron cited by the Examiner. Such CpGs of the CpG island sequence are readily identifiable and analyzable because they are structurally defined as being within SEQ ID NOS:36 or 37.

Moreover, as appreciated by the Examiner, the level of skill in the art at the time of filing was and is high, and given the instant teachings and those of the art, isolation of such a CpG island sequence from a cancer tissue and the determination of the methylation state of one or more CpG residues therein relative to a control, could be done by one of ordinary skill in the art at the time of filing in a matter of a few days or a week using routine, standard DNA manipulation methods and methylation assays available at the time of filing of the present application.

The Declaration by Dr. Kurt Berlin (already of record) is in support of the present Response and Amendment. The Declaration describes a paper (Eckhardt et al., *Nat Genet.* 2006 Dec;38(12):1378-85, Epub 2006 Oct 29) further confirming, as was appreciated in the art at the time of filing and as taught in the instant specification, that there is a significant correlation for co-methylation within CpG dense regions (*e.g.*, CpG islands) over the distance of up to at least 1,000 nucleotides in each direction from a particular determined CpG (see, *e.g.*, page 2, column 2, first full paragraph, of Eckhardt, already of record). The Declaration, therefore, additionally comments on and rebuts the Examiner's contentions, based on Toyota et al., while supporting Applicants' contentions.

The fact that the Eckhardt paper cited in the Berlin Declaration was available six years after filing and stated that “our data suggest DNA methylation to be ontogenetically more stable than previously thought” does not indicate, as urged by the Examiner, that there was no appreciation for coordinate methylation at the time of filing, as the present record supports. *Ontogenesis* refers to the origin and development of an individual organism from embryo to adult and the statement in Eckhardt, therefore, indicates that methylation during ontogenesis is more stable than previously appreciated. The Examiner’s present characterization of this statement is, in the very least, questionable, strained, and misleading.

Applicants also reaffirm and reassert the Declaration of Dr. Cathv Lofton Day, already of record, which confirmed the presently claimed utilities.

In light of the scope of the claims, the teachings in the specification, the presence of specific working examples in the specification, the high level of skill of those in this art, the knowledge of those of skill in this art, and the predictability of the subject matter, it would not require *undue* experimentation for a person of skill in the art to practice the invention as claimed.

The Examiner’s position seems to be that unless each and every CpG in an island is coordinately methylated, then one would have to experimentally sort through the various CpGs of the island to find the coordinately methylated ones, and this would amount to undue experimentation.

Applicants remind the Examiner that under U.S. patent law, the proper inquiry with respect to scope of enablement under 35 U.S.C. §112, first paragraph, is whether it would require *undue* experimentation to make and use the subject matter as claimed.

Applicants point out that all of the Wands factors must be considered by the Examiner and not merely the *predictability* factor.

A considerable amount of experimentation is permissible, particularly if it is routine experimentation. As appreciated by the Examiner, the amount of experimentation that is permissible depends upon a number of factors, which include: the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability of the art, and the breadth of the claims. Ex parte Forman, 230 USPQ 546 (Bd. Pat. App. & Int’f 1986); see also In re Wands, 8 USPQ2d 1400 (Fed. Cir. 1988).

The Applicants respectfully submit that one of skill in the art could fully practice the present claims without undue experimentation and with a reasonable expectation of success, and that if any experimentation is required to practice the present claims, such experimentation is merely routine and not undue upon consideration of all of the *Wands* factors. The Examiner has offered no evidence to support that any such required experimentation is other than routine.

Applicants point out that the claims have already been clarified and limited by amending the relevant independent claims to recite specific “SEQ ID NOS: 36 and 37 (both CpG islands).” In light of the scope of the claims, the teachings in the specification, the presence of specific examples in the specification, the high level of skill of those in this art, the knowledge of those of skill in this art (as exemplified by the Examiner’s own cited literature), and the predictability of the subject matter, Applicants respectfully submit that one of skill in the art could readily make and use the presently claimed subject matter without undue experimentation.

Applicants have, nonetheless, in response to the Examiner’s comments at page 12 regarding “prognosis”, amended claims 1, 2, 13, and 15-19 to recite “diagnostic assay” and have deleted the recitation of “prognostic.”

Accordingly, for all of the aforementioned reasons, Applicants respectfully submit that the basis for this rejection has been overcome, and request that the rejection be withdrawn.

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CONCLUSION

In view of the foregoing amendments and remarks, Applicants respectfully request entry of the present Response and Amendment, and allowance of all pending claims. The Examiner is encouraged to phone Applicants' attorney, Barry L. Davison, to resolve any outstanding issues and expedite allowance of this application.

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